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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/493,427	01/29/2000	Patrick L. Iverson	0450-0025.30	2225

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EXAMINER
EPPS, JANET L

ART UNIT	PAPER NUMBER
1635	20

DATE MAILED: 07/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/493,427	IVERSON ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Ford, Ph.D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 May 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Amendment

2. The Declaration filed under 37 CFR 1.132 filed 5-01-03 is sufficient to overcome the rejection of claims 28-48 based upon 35 USC 103(a) set forth in the Office Action mailed 11-01-02. However, the Weller Declaration is not deemed to be sufficient to overcome the new grounds of rejection of claims 28-48 under 35 USC 103(a) set forth below, because the Weller Declaration did not address the fact that it was commonly known in the art prior to filing of the instant application, that morpholino oligomers comprising uncharged phosphoramidite intersubunit linkages, delivered at the site of angioplasty may be used to prevent restenosis. Applicant's Declaration does not address the fact that the prior art disclosed a means for designing oligomeric compounds, and a means for delivery, such that restenosis may be prevented in a subject, and in addition to this fact, oligonucleotides targeting c-myc were well known in the art to have function to inhibit restenosis if delivered to the site of injury in a patient. Although Applicants consistently refer to the Kutryk et al. (2002) reference, that suggests that c-myc antisense failed to show efficacy, Applicants have not provided evidence that the conditions disclosed in Kutryk et al. were identical to those disclosed in the Zalewski et al. US Patent No. 6,159,946, wherein the local transcatheter delivery of c-myc antisense oligomers in a standard restenosis model, significantly reduces the formation of neointima in the coronary vasculature after vascular injury (see Example 11). Therefore, since it is unclear if the identical conditions were used in Kutryk et al. in comparison to Zalweski et al. one of skill in the art would not

accept on its face that Kutryk et al. provides evidence of non-enablement in regards to the teachings of Zalewski et al.

Response to Arguments

3. Applicant's arguments, see Paper No. 19, filed 5-01-03, with respect to the rejection(s)of claim(s) 28-48 under 35 USC 103(a) have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of Zalewski et al. (US Patent 6,159,946) in view of Burger (WO 98/46740 A1), as set forth below.

Claim Rejections - 35 USC § 103

4. Claims 28-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zalewski et al. (US Patent No. 6,159,946) as discussed above in view of Kobayashi et al. Burger (WO 98/46740), Summerton et al., Agrawal et al.

Zalewski et al. discloses a method for preventing restenosis in a patient comprising the administration of an antisense oligonucleotide targeting c-myc to the site of injury in a patient., wherein said antisense oligonucleotide comprises 14 contiguous nucleotides of SEQ ID NO: 1 of the instant application (see (col. 15-16, example 11). However, Zalewski et al. does not teach the administration of a c-myc antisense oligonucleotides comprising the nucleotides sequence as set forth in SEQ ID NO: 1 of the instant application, nor does Zalewski et al. teach morpholino modified antisense compounds having an uncharged phosphorous containing intersubunit linkages. Zalewski et al. does not teach the administration of antisense oligonucleotides in a solution containing at least about 30 mg/ml of the antisense compound. Zalewski et al. does not teach the use of a derivatized antisense compound comprising a triethyleneglycol moiety, or a

stent comprising said antisense compound. In addition, Zalewski et al. does not teach wherein the intravascular stent (or catheter) is biodegradable.

Kobayashi et al. teach the use of antisense oligonucleotides targeting the translation initiation sites of c-myc. These antisense oligonucleotides suppressed the proliferation of MKN-45, a human gastric cancer-derived cell line, and DLD-1, a human colon cancer-derived cell line, in vitro and in vivo. The antisense oligonucleotides comprise phosphorothioate type modifications. The c-myc AO suppressed MKN-45 cell proliferation in vitro at concentration from 0.1-10 mM, and 70% of suppression was obtained with 3-10 mM concentration. The AO decreased the ratio of c-myc positive cells, and the intracellular concentration of c-myc mRNA. Intratumor injection of AO for c-myc (27 mer, AACGTTGAGGGGCATCGTCGCGGGAGG, 10 mM) suppressed the tumor growth of MKN-45 transplanted to the BALB/c mouse. The c-myc antisense oligonucleotide of Kobayashi et al. comprises the nucleotide sequence of SEQ ID NO: 1 of the instant application (abstract).

Burger (WO 98/46740 A1) describes a method of inhibiting restenosis in a patient comprising comprising the administration of an oligomeric molecule that inhibits the expression of a gene associated with the development of restenosis. The oligomeric compound is preferally a morpholino oligomer composed of morpholino subunit structures, wherein the structures are linked together by uncharged, phosphorous-containing linkages that join the morpholino nitrogen of one subunit to the 5'-exocyclic carbon of an adjacent subunit. Preferably, the phosphorous containing linkages are phosphoramidite linkages (see bridging paragraph of pages 2-3). Additionally, Burger teaches that the oligomeric molecule may be preferably administered to a subject at the site of angioplasty via a perforated or porous catheter balloon, or within a

biocompatible polymeric carrier, which may be a hydrogel, e.g. an ethylene oxide/propylene oxide block copolymer. The carrier may also form all or part of an implanted endovascular support device or biodegradable stent (see page 9, lines 1-20).

Agrawal et al. teach modifications which enhance oligonucleotide solubility. In one embodiment Agrawal et al. discloses oligonucleotides comprising a triethyleneglycol moiety (col. 4, lines 8-12).

It would have been obvious to one of ordinary skill in the art at the time of filing of the instant application to modify the method of preventing restenosis in a patient as described by Zalewski et al. with the antisense oligonucleotide of Kobayashi et al. because this antisense oligonucleotide has been disclosed to function successfully in vitro and in vivo to reduce the expression of c-myc. Furthermore, one of skill in the art would have been motivated to use the antisense oligonucleotides of Kobayashi et al. because it would have been obvious to replace one functionally equivalent antisense oligonucleotide targeting c-myc with another.

It would have been obvious to one of ordinary skill in the art at the time of filing to modify the method of Zalewski et al. to comprise the administration of antisense oligonucleotides comprising internucleoside linkages having morpholino modifications and uncharged phosphorous modifications, and to comprise the use of a biodegrable stent as taught by Burger. One of ordinary skill in the art would have been motivated to use the morpholino oligomers of Burger in the method of Zalewski et al., because method of administration via biodegradable stent comprising oligomers having the morpholino structure of Burger were disclosed as being useful in reducing restenosis in an animal.

Moreover, it would have been obvious to one of ordinary skill in the art to further modify the oligonucleotides of Zalewski et al. with triethyleneglycol modifications as described by Agrawal, because these modifications enhance the solubility of the antisense oligonucleotides. Furthermore, one of ordinary skill in the art would have been motivated to use antisense oligonucleotides having enhanced solubility as modified by the method of Agrawal et al. since these antisense oligonucleotides are to be used in an aqueous biological environment. Agrawal et al. also teach that these moieties can be used to form oligonucleotide multimers, such multimers would enhance the effective concentration of the oligonucleotide and therefore increase the efficacy of an antisense compound. Burger also describes the use of polyethylene oxide block copolymers as a drug delivery device, see page 9, lines 7-9, therefore triethyleneglycol modifications would have been expected to enhance the delivery of antisense compounds into cells.

Applicant's method recites the use of an antisense compound in an amount of about 5 to 20 mg or in a solution containing at least about 30 mg/ml. Zalewski et al. teach the use of antisense oligonucleotides in their disclosed methods in amount of between about 1 to 100 μM and more preferably between 1 to 10 μM. Although the method of Zalewski et al. does not recite the exact amount of antisense compound as recited in Applicant's method, absent evidence to the contrary it would have been obvious to one of ordinary skill in the art to optimize the conditions of an experiment or reaction in order to maximize the desired results.

Therefore, the invention as a whole is *prima facie* obvious over Zalewski et al. (US Patent 6,159,946) in view of Kobayashi et al., Burger, Agrawal et al.

Conclusion

5. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford, Ph.D. whose telephone number is 703-308-8883. The examiner can normally be reached on M-T, Thurs-Fri, 8:30AM-6:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 703-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-746-5143 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Janet L. Epps-Ford, Ph.D.
Examiner
Art Unit 1635

JLE
July 10, 2003

Karen Lacourciere
KAREN LACOURCIERE
PATENT EXAMINER